II. Claims 1, 3, 6, 8-17, 22-24, drawn to an antagonist that inhibits angiogenesis by modifying protein-protein interactions comprising α5β1, classified in class 530, subclass 387.1.

III. Claims 1-2, 4-5, 7-13, 19-21, drawn to an antagonist that inhibits angiogenesis by modifying protein-protein interactions wherein the first protein is MMP-9 and the second protein is a β1-containing integrin, classified in class 536, subclass 22.1.

IV. Claims 1, 3, 6, 8-13, 19-21, drawn to an antagonist that inhibits angiogenesis by modifying protein-protein interactions comprising α5β1, classified in class 536, subclass 22.1.

V. Claims 1-2, 4-5, 7-13, 18, drawn to an antagonist that inhibits angiogenesis by modifying protein-protein interactions wherein the first protein is MMP-9 and the second protein is a β1-containing integrin, classified in class 530, subclass 300+.

VI. Claims 1, 3, 6, 8-13, 18, drawn to an antagonist that inhibits angiogenesis by modifying protein-protein interactions comprising α5β1, classified in class 530, subclass 300+.

VII. Claims 25-28, drawn to a polypeptide for inhibiting angiogenesis and/or tumor growth that specifically binds MMP-9 with a binding affinity greater than the binding capacity of SEQ ID NO:3 to MMP-9, classified in class 514, subclass 2.

VIII. Claims 25, 29-30, drawn to a monoclonal antibody for inhibiting angiogenesis and/or tumor growth that specifically binds MMP-9 with a binding affinity greater than the binding capacity of SEQ ID NO:3 to MMP-9, classified in class 530, subclass 388.1.

IX. Claims 31-34, drawn to a polypeptide for inhibiting angiogenesis and/or tumor growth that specifically binds a β1-containing integrin with a binding affinity greater than the binding capacity of SEQ ID NO:3 to the β1-containing integrin, classified in class 514, subclass 2.

X. Claims 31, 35-36, drawn to a monoclonal antibody for inhibiting angiogenesis and/or tumor growth that specifically binds a β1-containing integrin with a binding affinity greater than the binding capacity of SEQ ID NO:3 to the β1-containing integrin, classified in class 530, subclass 388.1.

XI. Claims 37-42, drawn to an antagonist that specifically binds with SEQ ID NO:1, but also binds to SEQ ID NO:3 with reduced affinity, classified in class 514, subclass 2.

XII. Claims 37-40, 43-44, drawn to a monoclonal antibody that specifically binds with SEQ ID NO:1, but also binds to SEQ ID NO:3 with reduced affinity, classified in class 530, subclass 388.1

XIII. Claims 45-50, drawn to a protein antagonist that disrupts the localization of MMP-9 on a cell surface or blood vessel, classified in class 530, subclass 300.

XIV. Claims 45-48, 51-52 drawn to a monoclonal antibody that disrupts the localization of MMP-9 on a cell surface or blood vessel, classified in class 530, subclass 388.1.

XV. Claims 53-59, drawn to a method of inhibiting angiogenesis comprising administering an antagonist, classified in class 424, subclass 184.1.

XVI. Claims 60-64, drawn to a method of inhibiting tumor growth comprising administering an antagonist, classified in class 424, subclass 184.1.

XVII. Claims 65-68, drawn to a method of inhibiting psoriasis, mascular degeneration, or restenosis in a tissue comprising administering an antagonist, classified in class 424, subclass 184.1.

XVIII. Claims 69-72, drawn to a method of detecting angiogenesis in a tissue by contacting an antagonist with said tissue, classified in class 424, subclass 9.1.

XIX. Claims 73-76, drawn to a method of detecting tumors or tumor invasion by administering an antagonist, classified in class 424, subclass 9.1.

XX. Claims 77-80, 85-88, drawn to a method of screening for MMP-9 antagonists comprising providing a non-peptide antagonist and measuring said antagonist's affinity for binding with MMP-9 and SEQ ID NO:3, classified in class 435, subclass 4.

XXI. Claims 77, 81, 85-88, drawn to a method of screening for MMP-9 antagonists comprising providing a peptide antagonist and measuring said antagonist's affinity for binding with MMP-9 and SEQ ID NO:3, classified in class 435, subclass 4.

XXII. Claims 77, 82-88, drawn to a method of screening for MMP-9 antagonists comprising providing an antibody antagonist and measuring said antagonist's affinity for binding with MMP-9 and SEQ ID NO:3, classified in class 435, subclass 7.1.

XXIII. Claims 89-92, 97-100 drawn to a method of screening for β1 integrin antagonists comprising providing a non-peptide antagonist and measuring said antagonist's affinity for binding with a β1 integrin and SEQ ID NO:3, classified in class 435, subclass 4.

XXIV. Claims 89, 93, 97-100 drawn to a method of screening for β1 integrin antagonists comprising providing a peptide antagonist and measuring said antagonist's affinity for binding with a β1 integrin and SEQ ID NO:3, classified in class 435, subclass 4.

XXV. Claims 89, 94-100 drawn to a method of screening for β1 integrin antagonists comprising providing an antibody antagonist and measuring said antagonist's affinity for binding with a β1 integrin and SEQ ID NO:3, classified in class 435, subclass 7.1.

XXVI. Claims 101-104, drawn to a peptide comprising a sequence encoding an epitope recognized by a monoclonal antibody, classified in class 530, subclass 300.

Applicants believe that, at least with respect to Groups I-XIV and XXVI, the restriction requirement does not comply with MPEP §803 because there would not exist "a serious burden on the examiner if restriction is not required." The guidelines to MPEP §803 indicate that the *prima facie* of a serious burden may be shown by a separate classification, or a separate status in the art, or a different field of search. The Examiner failed to make such a showing.

The classification and content of Groups I-XIV and XXVI largely overlap. The Examiner has indicated that the claims of Groups I, II, V, VIII, X, XII-XIV, and XXVI are classified in the same class 530. Additionally, Groups I and II are classified in the same subclass 387.1; Groups VIII, X, XII, and XIV are classified in the same subclass 388.1; and Groups V, VI, XIII, and XXVI are classified in the same subclass 300. Similarly, the Examiner noted that the claims of the remaining Groups III and IV are classified in the same class 536 and subclass 22.1; Groups VII, IX, and XI are classified in the same class 514 and subclass 2; and Groups III and IV are classified in the same class 536 and subclass 22.1. Additionally, the restricted Groups I-VI largely overlap. For example, Group II contains only the two additional claims 3 and 6 as compared to Group I. Similarly, Group V contains only the one additional claim 18 as compared to Groups I and III.

Furthermore, the inventions of Groups I-XIV and XXVI are related and have not acquired a separate status in the art. Independent claim 1 is directed to an antagonist that inhibits angiogenesis by modifying protein-protein interactions. Claims 2-24 and 101-104 depend from claim 1 and provide additional limitations on the proteins and their interaction. For example, claims 2, 4-5, and 7 require that one of the proteins is MMP-9, while claims 3 and 4-7 require that one of the proteins is a β1-containing integrin. Claims 101-104 are directed to a peptide comprising a sequence encoding an epitope recognized by an antagonist of claim 1.

Independent claim 25 and its dependent claims 26-30 are directed to a polypeptide that specifically binds to MMP-9. Independent claim 31 and its dependent claims 32-36 are directed to polypeptides (claims 32-34), including monoclonal antibodies (claims 35-36) that specifically bind to a β1-containing

integrin. Independent claim 37 and its dependent claims 38-44 are directed to an antagonist (claims 48-42), such as monoclonal antibody (claims 43-44), that specifically binds with SEQ ID NO:1 (a peptide mediating interaction between MMP-9 and α5β1 integrin, *see* page 7, lines 23-27, of the specification). Independent claim 45 and its dependent claims 46-52 are directed to an antagonist (claims 46-50), such as monoclonal antibody (claims 51-52), that disrupts the localization of MMP-9 on a cell surface or blood vessel.

Therefore, the subject matter of the claims in Groups I-XIV and XXVI relates to MMP-9 and β1-containing integrins. As explained on page 7, lines 17-22, MMP-9 binds directly with the β1-containing integrin and cells lacking the gene for making β1 integrins have a considerably reduced capacity for binding MMP-9. Also, both MMP-9 and α5β1 (one of specific examples of β1-containing integrins) are associated with human vascular compartment and tumor cells. Accordingly, the inventions of all Groups I-XIV and XXVI are related and have not acquired a separate status in the art. In fact, the art required to be searched for all of these inventions largely overlaps and includes MMP-9 and β1-containing integrins. Accordingly, Applicants believe that the Examiner failed to show a serious burden that requires the restriction of the claims into Groups I-XIV and XXVI.

Similarly, Applicants believe that claims 53-76 directed to the use of the antagonist of claim 1 should be examined as one group. Also, claims 77-100 directed to the methods of screening for MMP-9 and β1 integrin antagonists should be examined together.

Public policy strongly favors changing the twenty-six-way restriction imposed by the Examiner to a three-way restriction proposed by the Applicants. In particular, the fifteen-way restriction imposed by the Examiner on claims 1-52 and 101-104 (Groups I-XIV and XXVI) represents an undue burden on the Applicants, on the Patent and Trademark Office (PTO), and on the public. If the Restriction Requirement stands, the Applicants will be required to file a total of fifteen applications based on a set of 56 related claims. For each filed application, Applicants will have to pay filing, issue, and maintenance fees. This undue

multiplication of fees does not "promote the progress of useful arts", as required by Article 1, §8, col. 8, of the Constitution. Forcing the Applicants to file and prosecute fifteen separate patent applications will not promote the policy favoring patent protection and exploitation.

Additionally, the filing of fifteen separate patent applications will greatly increase the burden on the PTO, as it will require fifteen separate searches of the relevant art with largely overlapping results. Additionally, the PTO will have to process fifteen identical Information Disclosure Statements and sets of Figures. Furthermore, the PTO will have to coordinate the prosecution of the fifteen applications to ensure that the addition of new claims and the amendment of the existing claims in one application does not create a problem of double patenting in another application. Therefore, the workload of the PTO will greatly increase as a result of the restriction requirement imposed by the Examiner.

Finally, the existence of the closely related, fifteen separate patents will hinder the ability of the public to determine the scope of the patented subject matter and the areas of the art open for further exploration.

Accordingly, the Examiner is respectfully requested to regroup claims into three groups: Product - Group I (claims 1-52 and 101-104), Method of Use - Group II (claims 53-76), and Method of Making - Group III (claims 77-100). Alternatively, if the Examiner finds the three-way restriction inappropriate, Applicants request at least examining claims 1-24 (Groups I-VI) together.

In view of all of the above, examination of the present application on the merits is respectfully requested.

Respectfully submitted,
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